cartilage-derived cell, an invasive pannus-derived cell, a T lymphocyte, a B lymphocyte, a mast cell, a macrophage, a plasma cell, a dendritic cell and a natural killer cell.

55. (New) The method of claim 1, wherein the cadherin-11 counter-receptor is a component of an extracellular matrix of a tissue, a cartilage or a bone.

56. (New) The method of claim 1, wherein the cadherin-11 counter-receptor is a molecule secreted by a cell.

Remarks

The specification is amended to remove explicit recitation of internet addresses, and to replace these addresses with the descriptor "NCBI/NIH website". The addresses removed are clearly NCBI/NIH addresses and the accompanying, originally filed text identifies the addresses as NCBI internet addresses. Accordingly, no new matter has been introduced.

Claims 1 and 44 have been amended to recite that the cadherin-11 inhibitory agent is an antibody that binds to cadherin-11. These amendments are consistent with the restriction election made previously. (See Response dated February 15, 2002.)

Claims 7, 9, 13, 22, 24, 25, 30, 35, 36, 46, 48 and 49 are cancelled herewith as drawn to non-elected inventions.

Claim 8 is also cancelled and its subject matter has been incorporated in part into claims 1 and 44.

New claims 50-56 have been introduced. These claims were previously cancelled in order to reduce fees. Support for these claims can be found in the originally filed claims as follows:

New claim number	Originally filed claim number
50	2
51	4
52	17
53	18
54	19
55	20
56	21

Claims 1, 3, 5-6, 16, 44-45, and 50-56 are currently pending.

No new matter has been added.

Claim Fees

Applicants previously paid for 20 total claims and 6 independent claims. In view of the claim cancellations and additions recited above, there are now 14 total claims and 2 independent claims pending. Accordingly, no additional claim fees are considered due.

Declaration for Patent Application and Updated Application Data Sheet

Applicants provide herewith a new Declaration for Patent Application signed by inventor Xavier Valencia. This Declaration is intended to replace the previously submitted Declaration that was considered defective by the Examiner. The Declaration indicates that Dr. Valencia's citizenship and new home address. An updated Application Data Sheet is also submitted herewith to reflect the address change.

Rejection under 35 U.S.C. §112, first paragraph, enablement

Claims 1, 3, 5, 6, 16 and 44-45 have been rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a method for treating a subject having a rheumatoid arthritis disorder comprising administering locally to a synovium of the subject an anti cadherin-11 monoclonal antibody does not reasonably provide enablement for a method for treating a subject having any inflammatory joint disorder comprising administering any cadherin-11 agent."

Applicants respectfully traverse this rejection in view of the claim amendments and the reasons set forth below.

i. Genus/Species Enablement:

The Examiner believes the genera of inflammatory joint disorders and anti-cadherin-11 antibodies are not enabled, but that the species of rheumatoid arthritis and anti-cadherin-11 monoclonal antibodies are enabled by the specification. The MPEP states that "for a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner

without undue experimentation." (MPEP §2164.02.) As discussed in greater detail below, the representative examples of antibodies and inflammatory joint diseases provided in the specification, the similarities between these species and their respective genera, and the state and level of skill in these arts support the assertion that one of ordinary skill in these arts would expect the genera to be used in the claimed manner without undue experimentation.

a. Inflammatory Joint Disorders:

The Examiner states that the specification is enabling for treatment of rheumatoid arthritis but not other inflammatory joint disorders. Applicants traverse this on the basis that inflammatory joint disorders, of which rheumatoid arthritis is a species, share several pathological, mechanistic and therapeutic characteristics. Similar symptoms and/or pathologies are observed in inflammatory joint disorders, including signs of inflammation (e.g., erythema, warmth, pain and swelling), systemic symptoms (e.g., prolonged morning stiffness, fatigue, fever, and weight loss), laboratory evidence of inflammation (e.g., elevated erythrocyte sedimentation rate or C-reactive protein level, thrombocytosis, anemia of chronic disease, hypoalbuminemia, the presence of inflammatory effusion with white blood cell counts of greater than 2000/μL). Most importantly, the histopathology which reflects the tissue abnormalities and nature of the tissue injury in these disorders is indistinguishable and is characterized by synovitis with inflammatory, proliferative and in severe cases, erosive changes. The terms "synovitis" and "inflammatory arthritis" (as opposed to degenerative or osteoarthritis) are commonly used to refer to a group of disorders that affect the same regions of the body (i.e., joints) and involve similar cell types (e.g., including synoviocytes, and immune cells or inflammatory leukocytes). These disorders include but are not limited to psoriatic arthritis, ankylosing spondylitis, reactive arthritis, systemic lupus erythrematosus and the arthritides associated with inflammatory bowel disease and infectious disease such as hepatitis. Underlying mechanisms are also thought to be common, and these include involvement of the immune system. Finally, treatments that are therapeutically effective for rheumatoid arthritis have been shown to be effective in other inflammatory joint disorders. These therapies include treatment with TNF-α neutralizing agents (e.g., infliximab and etanercept) and methotrexate. In view of the art-recognized similarity between inflammatory joint disorders, the ability to treat such diseases with similar agents, and

the acknowledged enablement of the treatment of one species of this genus, Applicants maintain that treatment of the genus as a whole is similarly enabled.

b. Cadherin-11 Inhibitory Agent:

Independent claims 1 and 44 have been amended to recite that the cadherin-11 inhibitory agent is an antibody to cadherin-11. The claimed methods therefore embrace the genus of antibodies that bind to cadherin-11. The Examiner states that only monoclonal antibodies are enabled, but provides no support for this assertion.

The specification teaches the genus of antibodies and provides specific examples of monoclonal antibodies to cadherin-11. The state of the art of antibody generation and use is advanced. (See for example the USPTO Written Description Guidelines, Example 16 which states that "the level of skill and knowledge in the art of antibodies ... was such that production of antibodies against a well characterized antigens was conventional ... This is a mature technology where the level of skill is high and advanced... Considering the routine-art recognized method of making antibodies to fully characterized antigens ..") Cadherin-11 is an example of a "fully characterized antigen" and thus the production of antibodies to it would be considered routine by the art. One of ordinary skill would know how to make antibodies, including polyclonal antibodies, to cadherin-11 and how to use such antibodies given the teaching in the specification and level of skill in the art. One of ordinary skill expect that the entire genus of antibodies to cadherin-11 could be made and used according to the teaching of the specification without undue experimentation.

Further proof of enablement of the remaining species of the genus is required only if the Examiner provides adequate reasons for why a person skilled in the art could not use the genus as a whole without undue experimentation. (MPEP § 2164.02.) The Examiner is respectfully requested to advance such reasons or withdraw the rejection.

ii. Therapeutic Efficacy:

The Examiner states that "the problem (with the use of monoclonal antibodies to cadherin-11) would be how many times the administration of the antibodies are repeated and needed" and that therapeutic efficacy "will vary depending upon factors such as the condition of

the host and burden of inflammatory joint disorder." The Examiner maintains that the related arts are unpredictable and thus "more specific enablement is necessary."

The art is familiar with treatment of inflammatory joint disorders. (See, for example, Harrison's Principles of Internal Medicine, and Ruddy: Kelley's Textbook of Rheumatology, 6th ed., Copyright © 2001 W. B. Saunders Company .) The art is also familiar with antibody therapies, particularly relating to inflammatory joint diseases (e.g., antibodies such as infliximab, D2E7 (anti-TNF mAb, Abbott Laboratories), Rituximab, and anti-Fas ligand (see '877 patent discussed below) have been described for use in the treatment of inflammatory joint diseases). Accordingly, antibodies directed to targets other than cadherin-11 are in common use. These include monoclonal antibodies made in various species, chimeric monoclonal antibodies in which different parts of the antibody (e.g., framework and CDR regions) derive from different species, and variously engineered monoclonal antibodies (e.g., those in which the amino acid or nucleic acid sequence is changed to affect binding affinity, pharmacokinetics, bioavailability or other immunological features). The specification provides guidance for antibody amounts, administration routes and formulations. (See, for example, pages 33-39, where it is taught that the effective amount will "depend upon the stage of the condition, the severity of the condition, the age and physical condition of the subject being treated, the nature of concurrent therapy, if any, the duration of the treatment, the specific route of administration and like factors **within the knowledge and expertise of the medical practitioner**." (emphasis added).)

Accordingly, a medical practitioner (i.e., one of ordinary skill in the art) will be able to determine the therapeutic amount of antibody to be administered, the number of administrations necessary and the administration route most suitable. Applicants respectfully point out that patentability does not require a demonstration of human testing. Human testing is a requirement of the FDA, not the Patent Office. (See MPEP § 2164.05.)

iii. In vitro and In vivo Correlation:

The Examiner states that the claims are not enabled because the only data provided in the specification relate to in vitro adhesion assays using human type B synoviocytes. The Examiner claims that it is unpredictable how to correlate test tube results with in vivo clinical efficacy.

The issue of correlation between the in vitro results and in vivo methods centers on whether the examples can be considered working examples. Although Applicants assert that the

specification provides working examples, it is respectfully pointed out that the absence of a working example is not sufficient to render an invention non-enabled if all other factors point toward enablement. (See MPEP § 2164.02.) Applicants traverse the enablement rejection because the specification, as a whole, together with the level of skill in the art points towards enablement.

Whether the in vitro data presented correlates with the claimed methods is dependent on the state of the prior art (i.e., "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate"). (See MPEP § 2164.02.) The ultimate determination is whether one of skill in the art would accept the model as reasonably correlative.

The examples provided are correlative with the claimed methods. The specification shows that cadherin-11 antibody staining indicates that cadherin-11 is expressed preferentially in the lining cells of rheumatoid arthritis synovium. The specification further teaches that anti-cadherin-11 antibody can be used to inhibit binding of T cells and B cells to cadherin-11 Fc fusion protein.

The claimed methods relate to treatment of subjects having an inflammatory joint disorder (of which rheumatoid arthritis is an example) by administering to the subject a therapeutically effective amount of an antibody to cadherin-11 that inhibits binding of cadherin-11 to a cadherin-11 counter-receptor, or that modulates a cellular function in a cadherin-11 expressing cell. Although not intending to be solely bound by any particular theory, some of the claimed methods require at least in part that the administered antibody inhibit binding of cadherin-11 to its counter-receptor. This has been demonstrated by the in vitro data provided.

Notwithstanding the foregoing, however, Applicants submit herewith further experimental evidence to demonstrate the enabling nature of the specification as filed. These data were generated by experiments conducted in accordance with the teaching in the specification and thus they establish that the specification was enabling as of the time of filing. (See Appendix B.) The data demonstrate that cadherin-11-Fc fusion protein parenterally administered to mice having serum-induced arthritis caused reduction in clinical symptoms of inflammatory arthritis including reduced ankle thickness, delay in arthritis onset, and decreased maximal arthritic index. The data confirm the teaching in the specification that inhibition of cadherin-11 interaction with its counter-receptor (whether by cadherin-11-Fc fusion protein or

anti-cadherin-11 antibody) ameliorates inflammatory arthritis, as shown in a murine arthritis model.

Accordingly, in view of the teaching in the specification, the level skill in the art, and the demonstration of an in vivo model showing therapeutic efficacy based on the teaching of the specification, one of ordinary skill in the art would consider the claimed invention enabled at the time of filing.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph, enablement.

Rejection under 35 U.S.C. §112, first paragraph, written description

Claims 1, 3, 5, 6, 16 and 44-45 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to the Examiner, "Applicant is in possession of a method for treating a subject having a rheumatoid arthritis comprising administering locally to a synovium of the subject an anti cadherin-11 monoclonal antibody, however applicant is not in possession of a method for treating a subject having any inflammatory joint disorder comprising administering any cadherin-11 agent .... Conception in the above cases cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method."

Applicants respectfully traverse the rejection for the reasons provided below.

As amended, the claims require administration of an antibody to cadherin-11. The use of other forms of cadherin-11 inhibitory agents was previously restricted from the claimed invention. As provided in the Written Description Guidelines referred to by the Examiner, "the general knowledge in the art is such that antibodies are structurally well characterized" ... and "it is well known that antibodies can be made against virtually any protein." (See Written Description Guidelines, Example 16.)

Similarly, as discussed above, the genus of inflammatory joint diseases shares a number of similarities, known to those of skill in the art, including common symptoms, pathology, and therapies.

Accordingly, in view of the claim amendments presented herewith and the level of skill in the art, the specification provides a sufficient written description of both the antibody and inflammatory joint disorder genera.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph, written description.

Valencia et al. Abstract

Applicants previously cited the Valencia et al. abstract in an Information Disclosure Statement and Form 1449 filed December 5, 2000 (Valencia et al. Identification of Cadherin-11 in Type B Synoviocytes Derived from Rheumatoid Arthritis Patients" Abstract Submission Form – ACR 62nd National Meeting, Nov 8-12, 1998, San Diego, CA). Applicants later submitted a copy of the International Search Report issued by the PCT Office in the corresponding PCT application (cited to USPTO on April 16, 2001). The International Search Report provides a September 1998 date for the abstract. Applicants are currently uncertain as to the publication date of this abstract. (See, for example, the Volume Data Sheet provided from the publisher of Arthritis and Rheumatism, attached herewith, indicating that the "label date" is September 1, 1998.) Although this abstract may not be prior art against the claims, Applicants will present arguments that demonstrate the patentability of the claims in view of the abstract in order to advance prosecution.

Rejection under 35 U.S.C. § 103(a)

i. US Patents 6,086,877 and 5,597,725 and Valencia et al.:

Claims 1, 3, 5, 6, 8, 16 and 44-45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 6,086,877 in view of U.S. Patent 5,597,725 (IDS reference A1) and Valencia et al. (IDS reference C2). According to the Examiner, the '877 patent teaches a method of treatment for rheumatoid arthritis comprising administering to a patient an amount of an anti-Fas monoclonal antibody for treating rheumatoid arthritis. According to the Examiner, the '725 patent teaches methods for inhibiting binding of cadherins to their natural ligands/anti-ligands by contacting a cadherin with an antibody such as a monoclonal antibody capable of specifically binding to cadherin-11. The Examiner relies on the Valencia reference for, inter

alia, the identification of cadherin-11 in type B synoviocytes derived from rheumatoid arthritis patients. Applicants respectfully traverse the rejection for the reasons stated below.

The '877 patent teaches the use of anti-Fas ligand antibodies in the treatment of rheumatoid arthritis (RA). The patent reports detection of Fas ligand in the synovium of RA patients. While the patent states that inhibition of synovial cell proliferation can be therapeutically effective, it teaches that the anti-Fas ligand antibody works by inducing apoptosis of synovial cells. The patent further teaches the combination of the anti-Fas ligand antibody and an agent that inhibits proliferation.

The '725 patent teaches nucleic acid and amino acid sequences of cadherins including cadherin-11. The patent further teaches a method for making antibodies to cadherins and states that such antibodies could be used to modulate natural binding and/or regulatory activities of cadherins. These regulatory activities are listed as neurite growth promoting activity, regulation of cell growth, embryonic cell adhesion, and epithial (sic) cell adhesion.

The Valencia et al. abstract teaches that cadherin-11 is present in synoviocytes of rheumatoid arthritis patients. The abstract states that cadherins maintain tissue architecture and are important signalling molecules. The abstract hypothesizes that "This cadherin *may* mediate homophilic adhesion between synoviocytes, which *could* influence synovial proliferation and pannus invasion into cartilage *or could* engage in a heterophilic interaction anchoring lymphocytes within the synovial membrane parenchyma" (emphasis added)." Moreover, the authors, two of whom are co-inventors of the instant application, state that they "*are assessing these possibilities*". The abstract therefore teaches nothing about the role of cadherin-11 in rheumatoid arthritis. It simply speculates on what cadherin-11 *may* do, and what the downstream of effects of this *could* be. To emphasize this point, the authors, two of whom are co-inventors of the instant application, indicate that they must still *assess* these *possibilities*. Accordingly, there is no guidance as to whether cadherin-11 does indeed modulate any of these activities; there is only a list of activities that cadherin-11 might affect. The abstract can only be viewed as an invitation to experiment in order to determine whether and which of these activities are indeed affected by cadherin-11. Applicants submit herewith a copy of the International Preliminary Examination Report which finds novelty and inventive step in examined claims 1-43 even in view of the Valencia et al. reference. (See Appendix D.) The claims are identical to claims 1-43 as originally filed in the instant application. Indeed, the PCT examining authority considered the

Valencia et al. abstract as an "A" reference indicating that it was a "reference defining the general state of the art which is not considered to be of particular relevance." Moreover, the PCT examining authority characterizes the Valencia et al. abstract as a reference that "refers to cadherins and to the synovium.., but only questions and possibilities arrive from this study." The examining authority concludes that "the skilled person starting from the teaching in this document would not unambiguously arrive to the method of claim 1." While Applicants are aware that the findings and opinion of the PCT examining authority is not controlling authority for the USPTO, it is however instructive as to how one of ordinary skill would interpret the Valencia et al. abstract.

The combination of the '877 and '725 patents and the Valencia et al. abstract does not render the pending claims obvious. To establish a prima facie case of obviousness, the following three requirements must be met: 1) there must be a suggestion or motivation to combine the teachings of the references relied upon; 2) there must be a reasonable expectation of success; and 3) the combination must recite each and every limitation of the pending claims. Applicants challenge the existence of a suggestion or motivation to combine the references, particularly since the agent of the '877 patent is one that induces apoptosis, and neither the '725 patent nor the Valencia et al. abstract discuss apoptosis. Applicants further challenge the existence of a reasonable expectation of success particularly in view of the highly speculative nature of the Valencia et al. abstract, and the opinion of the PCT examining authority that "the skilled person ... would not ambiguously arrive to the method of claim 1". The combination can only amount to a mere invitation to experiment further to determine which, if any, of the proposed mechanisms actually involve cadherin-11. In view of the speculative nature of the Valencia et al. abstract, one of ordinary skill would not have a reasonable expectation of success. The Examiner is reminded that both the motivation to combine and the reasonable expectation of success must be found in the prior art references and not in the instant application. The Examiner must take "into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made" and must not "include knowledge gleaned only from the applicant's disclosure." MPEP § 2145.

The motivation to combine and the reasonable expectation of success do not exist, and thus the burden of establishing a prima facie case of obviousness has not been satisfied.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103 (a).

ii. US Patents 6,086,877 and 5,597,725 and Valencia et al. and US Patent 5,886,026:

Claims 45 is rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 6,086,877 in view of U.S. Patent 5,597,725 (IDS reference A1), Valencia et al. (IDS reference C2), and U.S. Patent 5,886,026. The rejection in view of the first three references is as stated above. According to the Examiner, the '026 patent teaches that numerous enzymes are likely involved in rheumatoid arthritis and numerous cell types found in the arthritic joint such as synoviocytes are capable of synthesizing and secreting matrix metalloproteinases. The Examiner concludes that one of ordinary skill would have been motivated to substitute the anti-Fas monoclonal antibody with an anti-cadherin-11 antibody in order to modulate the cellular function such as MMPS secretion in the cell expressing cadherin-11 such as synoviocytes. Applicants respectfully traverse the rejection for the reasons stated below.

The rejection is traversed at least for the reasons set forth above. The combination of the '877 and '725 patents and the Valencia et al. abstract does not render the invention obvious for the reasons stated above. The '026 patent teaches agents, in particular paclitaxel, that are angiogenesis inhibitors. The patent teaches that pannus tissue cells, which include neovascular tissue, connective tissue and inflammatory cells, release digestive enzymes and other mediators of the inflammatory process, and that this release leads to the destruction of cartilage tissue. The patent however provides no teaching that cadherin-11 is involved in these processes, or more importantly, that blocking agents to this cadherin could influence such processes. This latter teaching is only found in the instant application. Accordingly, the addition of the '026 patent does not cure the deficiencies of the prior combination of references, particularly the motivation to combine and the reasonable expectation of success that is required for a prima facie case. For at least these reasons, the combination does not render claim 45 obvious.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a).

Summary

Applicants believe that each of the pending claims now is in condition for allowance. Applicants respectfully request that the Examiner telephone Applicants' agent in the event that the claims are not found to be in condition for allowance.

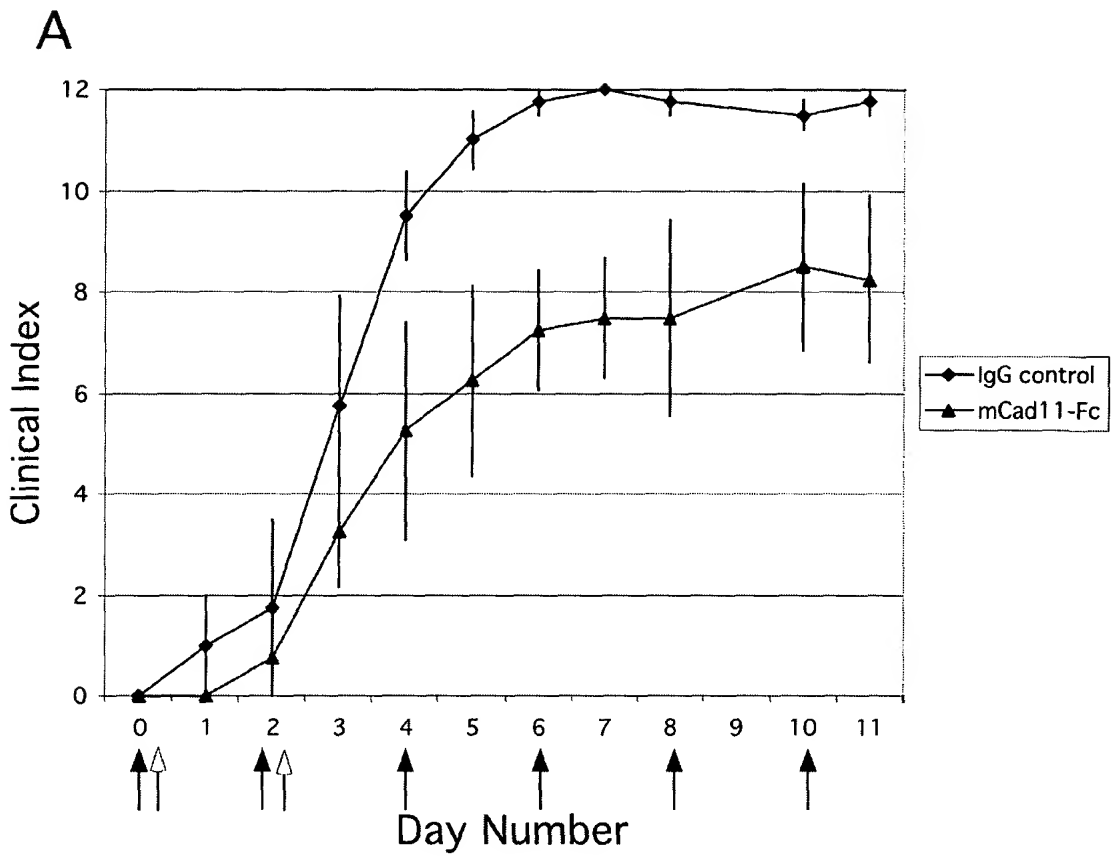
If the Examiner has any questions and believes that a telephone conference with Applicants' agent would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (extension 266).

Respectfully Submitted,

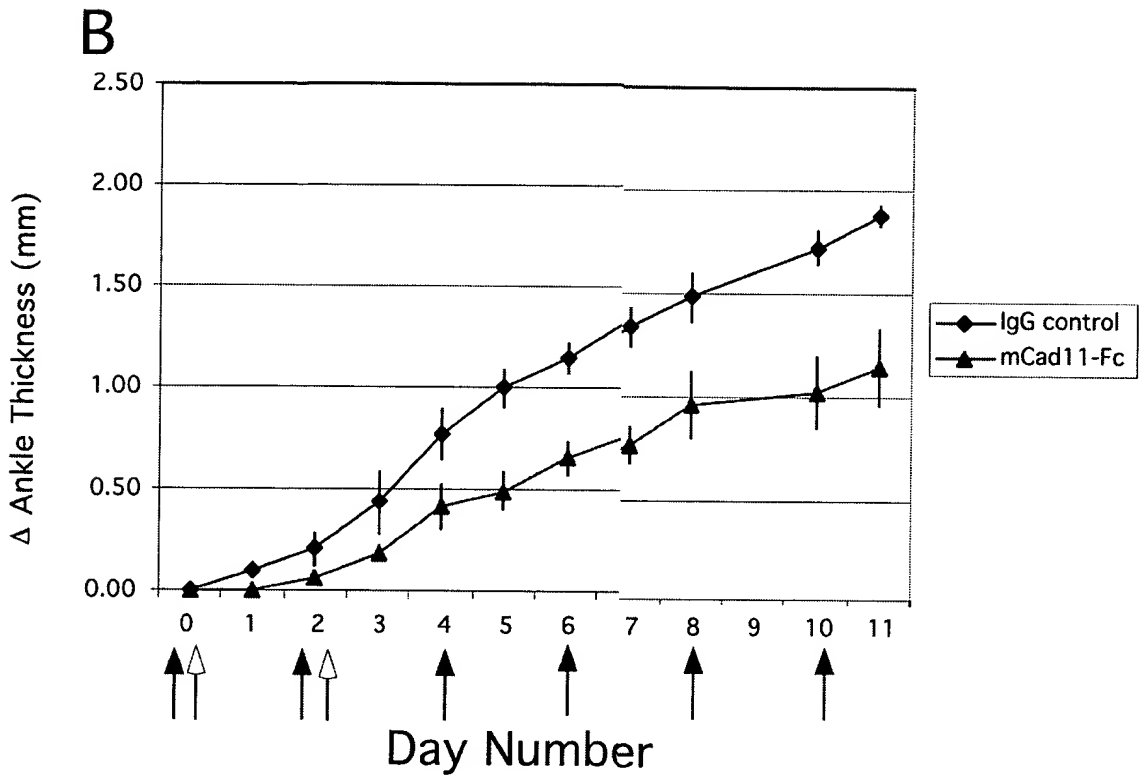
Maria A. Trevisan, Reg. No. 48,207
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210
Tel: (617) 720-3500

Docket No.: B00801.70187.US
Date: October 28, 2002
x10/26/02

Appendix B -page 1 of 2



Appendix B - page 2 of 2



In vivo effect of cadherin 11-Fc in inflammatory arthritis.
Cadherin 11-Fc (closed arrows) was administered coincidentally with KBxN arthritogenic serum (open arrows) and every 48 hours thereafter. (A) clinical index measurement. (B) change in ankle thickness. Values are reported as mean ± SEM. N=4 mice/group. Data are representative of 2 individual experiments.

Appendix A

Marked-up Specification

Please amend the paragraph beginning on page 24, line 4 as follows:

In general, cadherin-11 homologs and alleles typically will share at least 70% nucleotide identity with SEQ. ID. NO: 1; and in some instances, will share at least 75% nucleotide identity; and in still other instances, will share at least 80% nucleotide identity. Watson-Crick complements of the foregoing nucleic acids are also embraced by the invention. The preferred cadherin-11 homologs have at least 85% sequence homology to SEQ. ID. NO: 1. More preferably the cadherin-11 homologs have at least 90% and most preferably at least 95% sequence homology to SEQ. ID. NO: 1. The homology can be calculated using various, publicly available software tools developed by NCBI (Bethesda, Maryland) that can be obtained through the internet [(ftp:/ncbi.nlm.nih.gov/pub/)] at the NCBI/NIH website. Exemplary tools include the BLAST system available at [http://wwww.ncbi.nlm.nih.gov] the NCBI/NIH website. Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis can be obtained using the MacVetor sequence analysis software (Oxford Molecular Group).

Marked-up Claims

Please amend the claims as indicated below.

1. (Once Amended) A method for treating a subject having an inflammatory joint disorder comprising

administering to a subject in need of such treatment a therapeutically effective amount of a cadherin-11 inhibitory agent

wherein the cadherin-11 inhibitory agent is an antibody to cadherin-11 that inhibits binding of cadherin-11 to a cadherin-11 counter-receptor.

44. (Once Amended) A method for treating a subject having an inflammatory joint disorder comprising

administering to a subject in need of such treatment a therapeutically effective amount of an agent that is an antibody to cadherin-11 which modulates a cellular function in a cadherin-11 expressing cell.

Appendix C

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Date:21st October 2002

Fax Number: 9 001 6177202441

Pages including
this cover page: 2

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MESSAGE

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Georgina Dutt
Journals Fulfilment

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Journal : **ART** **Arthritis & Rheumatism** **IN STOCK**
Issue : **1998 Vol 41 Iss 9**

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Appendix D

...TENT COOPERATION TREATY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Subject to PTA? YES/NO per docket/ECB

To:

PLUMER, Elizabeth R.
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210
ETATS-UNIS D'AMERIQUE

See Legal Services Fax Copy

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ECB	☐
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Docket Cross Off	☑
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Date 10/10/01

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

#001 - 617 - 720 - 2441

Date of mailing *(day/month/year)*	27.09.2001
Applicant's or agent's file reference B0801/7187WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/24101	01/09/2000	03/09/1999

Applicant
THE BRIGHAM AND WOMEN'S HOSPITAL, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Neumann, M Tel.+49 89 2399-7351

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
B0801/7187WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/24101	01/09/2000	03/09/1999
International Patent Classification (IPC) or national classification and IPC A61K39/395		
Applicant THE BRIGHAM AND WOMEN'S HOSPITAL, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/03/2001	27.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer BROCHADO GARGANTA, M Telephone No. +49 89 2399 8935

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/24101

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-60 as originally filed

Claims, No.:

1-49 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

Sequence listing part of the description, pages:

1-8, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-21,44-49.

because:

   ☒ the said international application, or the said claims Nos. 1-21, with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*): **see separate sheet**

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 44-49.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/24101

1. Statement

Novelty (N)	Yes:	Claims	1-43
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-43
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	22-43
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 44-49 were not searched by the International Search Authority and therefore no opinion will be given for these claims.

2. Claims 1-21 relate to a method for treating an human being. They relate therefore to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   (A) WO 99 35166 A

   (B) X. Valencia et al.: Arthritis & Rheumatism, vol. 41, no. 9 suppl. (1998)

2. The following intermediate document, cited in the International Search Report ,will be of relevance for the examination of novelty and inventive step of the present application, if the priority date of the present application is not validly claimed:

   X. Valencia et al.: Arthritis & Reumathism, vol. 42, no. 9 suppl. (September 1999)

3. Novelty

   Claim 1, relating to a method for treating a subject having an inflammatory joint disorder, is new in the sense of Article 33(2) PCT, because such a method is not disclosed in the prior art. The same applies to dependent claims 2-43.

4. Inventive step

4.1 Document A discloses methods for using modulating agents to enhance or inhibit occludin-mediated cell adhesion, wherein the modulating agents comprise at least one occludin cell adhesion recognition sequence or antibody. Cadherins belong to the family of cell surface adhesion molecules (CAMs) (see pages 1-2 and abstract).

There is no indication in document A about a function of cadherin in inflammatory diseases. Moreover, no reference is made to cadherin-11.

While it has been known that cell adhesion molecules play a role in the adhesion of peripheral lymphocytes to endothelium, nothing is known regarding the mechanism by which lymphocytes transmigrate through the vascular endothelium to specifically target certain tissue location, such as the synovium.

Also document B refers to cadherins and to the synovium (see abstract), but only questions and possibilities arrive from this study, wherein for the first time there is a description of the presence of cadherin in the synovium: "the cadherin **may** mediate homophile adhesion between synoviocytes, which **could**...". The skilled person starting from the teaching in this document would not unambiguously arrive to the method of claim 1.

Thus, claim 1 is considered to be based on an inventive step (Article 33(3) PCT). the same applies to dependent claims 2-21.

4.2 Also the methods of claims 22 and 30 relating to methods for screening a molecular library to identify a pharmaceutical lad compound that modulates cadherin-11 mediated adhesion between a first cell that expresses cadherin-11 and a second cell that expresses a cadherin-11 counter-receptor, are also based on an inventive concept (Article 33(3) PCT), the reasons being those already given under 4.1. The same applies to dependent claims 23-29 and 31-43.

5. For the assessment of the present claims 1-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for

example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.